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REVIEW

Potential diagnostic markers for disseminated intravascular coagulation of sepsis

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ABSTRACT

Disseminated intravascular coagulation (DIC) is an acquired thrombo-haemorrhagic disorder which arises in clinical scenarios like sepsis, trauma and malignancies. The clinic-laboratory diagnosis of DIC is made in a patient who develops the combination of laboratory abnormalities in the appropriate clinical scenario. The most common laboratory parameters in this setting have been the clotting profile, platelet count, serum fibrinogen and fibrin degradation markers. These tests had the advantage that they could be performed easily and in most laboratories. However, with the better understanding of the pathophysiology of DIC, in recent years, more specific tests have been suggested to be useful in this setting. The newer tests can also prove to be useful in prognostication in DIC. In addition, they may provide assistance in the selection and monitoring of patients diagnosed with DIC.

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1. Introduction

The International Society of Thrombosis and Hemostasis DIC subcommittee defines DIC as “an acquired syndrome characterized by

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intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction" [1]. Currently, the diagnosis of DIC is based on the presence of laboratory features in patients with an underlying disorder which is known to be associated with DIC. These markers include the coagulation profile (prothrombin time [PT] and partial thromboplastin time [PTT]), platelet count, serum fibrinogen level, and a marker of fibrin degradation product like D-dimer or soluble fibrin monomer [2]. Although these tests are useful especially when used in conjunction and serially, they are not very specific or sensitive [3]. Until recently, although other laboratory markers were deemed useful, they were considered too specialized, requiring dedicated laboratories to perform the assays. In this review, we address the diagnostic ability of some laboratory assays and techniques to detect DIC, which can be done in the mainstream laboratories.

2. Measurement of endogenous anticoagulants

The main pathophysiological mechanism of DIC is the excessive thrombin generation. Thrombin also activates the natural anticoagulant pathway and as such plasma levels of two endogenous anticoagulants, antithrombin (AT) and protein C (PC) decrease significantly in patients with DIC and are useful in predicting the outcome of patients with sepsis and DIC [4,5]. The mechanisms responsible for the decrease in AT and PC activity in sepsis are thought to be consumption during activated coagulation, impaired synthesis in the liver, degradation by neutrophil elastase and other enzymes, and leakage from the endovascular space [6–9].

2.1. Antithrombin and Protein C

In patients with sepsis, multiple trauma, and major surgery, a correlation between the reduction in AT and disease severity has been shown [3,10]. For example, AT activity has been reported to be approximately 80% of normal in sepsis patients without organ dysfunction, decreasing to approximately 60% in patients with severe sepsis and 40% in patients with full-blown DIC [11]. Others have reported the diagnostic value for predicting patient outcome based on an area under the receiver operating characteristic curve (AUC) of the AT activity level or the PC activity level exceeding 0.8 [12–14]. Recently, Choi et al. [15] reported a significant negative correlation between AT and PC and the DIC score in patients with sepsis/severe sepsis, suggesting that these markers are good indicators of DIC severity. Indeed, AT and PC had a significant prognostic power in Kaplan–Meier analyses, and both markers showed higher hazard ratios than conventional coagulation markers such as D-dimer. For the early diagnosis of DIC, Koyama et al. [16] examined fourteen biomarkers in plasma including conventional markers (platelet count, PT and PTT, fibrinogen and fibrin degradation products), markers of thrombin generation (thrombin-antithrombin complex [TAT] and soluble fibrin), anticoagulants such as AT and PC, markers of fibrinolysis, and a marker of endothelial activation (soluble E-selectin) in 77 patients. Among them, TAT, plasminogen activator inhibitor-1 (PAI-1) and PC were capable of discriminating between patients with and without overt DIC with AUC value of 0.77 (95% confidence interval, 0.64–0.86), 0.87 (0.78–0.92), and 0.85 (0.76–0.91), respectively). They concluded that a single measurement of TAT, PAI-1, or PC activity could identify patients with ongoing severe coagulopathy from the early stage of sepsis. Yanagida et al. also reported similar results in trauma patients [17]. Though the measurements of PAI-1 and APC have not been routinely performed in most of the laboratories, there are many commercialized kits available. Total and free PAI-1 can be measured separately by different enzyme-linked immune-sorbent assay (ELISA). APC can be measured by antibody based ELISA and its activity is usually measured by the chromogenic substrate assay.

APC is known to bind its specific receptor endothelial protein C receptor (EPCR) on the endothelial surface and contributes to the local antithrombogenicity. The soluble EPCR can be another candidate for the biomarker of DIC because EPCR was reported to be shed in the circulation along with the endothelial damage [18]. However, the clinical value of circulating EPCR to predict disease progression and outcome still remains to be elucidated.

In addition to the ability to predict patient outcome, the other unique feature of these anticoagulant markers is their usefulness as a prognostic indicator after treatment. In a study of the efficacy of measuring AT activity in 192 septic DIC patients supplemented with AT, Iba et al. showed that not only the baseline AT activity level, but also the ΔAT activity (the AT value on Day 3 - the AT value on Day 0) were correlated with the patient outcome and DIC resolution [19]. Furthermore, a logistic regression test revealed that an increase in AT activity exhibited the highest contribution to patient survival and DIC resolution. Based on these reports, the AT activity-oriented dose selection have been recommended [20,21]. With regard to PC activity, it can be expected to become a marker of effectiveness after the treatment of thrombomodulin [22].

2.2. Thrombomodulin

Thrombomodulin is another anti-coagulant protein expressed on the surface of endothelial cells. It binds to thrombin, converts protein C into an active form and exhibits a range of physiologically important anti-inflammatory, anti-coagulant, and anti-fibrinolytic properties. Thrombomodulin plays an important role in attenuation of inflammatory responses, through inhibition of leukocyte adhesion to endothelial cells, inhibition of complement pathways, neutralization of lipopolysaccharide (LPS), and sequestration and degradation of pro-inflammatory high-mobility group box 1 protein (HMGB1) [23]. Endothelium-specific loss of thrombomodulin in mice causes spontaneous and fatal thrombosis in the arterial as well as venous circulation, suggesting that thrombomodulin is indispensable to prevent intravascular thrombus growth [24]. Cleavage of thrombomodulin occurs from the surface of endothelial cells into the circulation in part through proteolytic cleavage by neutrophil elastase in sepsis [25]. Plasma soluble thrombomodulin can be measured by the commercialized kits which are standard one-stage immunoassay using two monoclonal antibodies. This cleaved form of thrombomodulin is considered to be a marker for endothelial cell injuries and plasma thrombomodulin levels are elevated in patients with sepsis, and DIC, with higher levels in non-survivors compared with survivors [26,27]. The hypercoagulable state of DIC is marked by the elevation of plasma thrombomodulin with concomitant reduction of endothelial cell surface thrombomodulin in septic conditions [28]. The cofactor activity of these soluble fragments is generally 30–50% relative to that of membrane-bound thrombomodulin, although it ranges from zero to almost 100% depending on the size of the fragment [29,30].

A previous multicenter, double-blind, randomized trial to evaluate the efficacy and safety of recombinant human soluble thrombomodulin (rhsTM; ART-123) for the treatment of DIC, revealed that rhsTM therapy is more effective and safer than low-dose heparin, and rhsTM (Recomodulin α) was approved in Japan for the treatment of DIC in 2008 [31,32], and its beneficial effect has been reported [33]. rhsTM exhibits a range of anti-inflammatory, anti-coagulant, and anti-fibrinolytic properties, and an international, multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial for rhsTM (NCT01598831) is now on-going in the United States, European Union, and other countries throughout the world [32,34].

2.3. Tissue factor pathway inhibitor

Beside AT, PC, EPCR, and TM, tissue factor pathway inhibitor (TFPI) is also an important endogenous anticoagulant. TFPI is a primary regulator